UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/791,166	03/01/2004	Israel R. Charo	02307K-085041US	3893

20350 7590 06/27/2005

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 06/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/791,166	CHARO ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-13 and 15-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-13 and 15-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 March 2004* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/20/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendments and remarks filed 20 May 2005 have been entered. Claims 5 and 14 have been cancelled. Claims 1 – 4, 6 –13, and 15 – 17 are pending and under examination.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Priority

3. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

This application repeats a substantial portion of prior Application No. 09/625,573, filed 7/25/2000, Application No. 08/446,669, filed 5/25/1995, and Application No. 08/182,962, filed 01/13/1994, and adds new claims and additional disclosure not presented in the prior applications. Since this application names an inventor or inventors named in the prior application, it may constitute a continuation-in-part of the prior application. Should applicant desire to obtain the benefit of the filing date of the prior application, attention is directed to 35 U.S.C. 120 and 37 CFR 1.78.

The priority date of the instant application is the actual filing date, 1 March 2004.

Information Disclosure Statement

The IDS filed 20 May 2005 has been considered.

Withdrawn Rejections and Objections

4. The following rejections and objections made in a previous office action are hereby withdrawn:

The objections to the drawings. Applicant has amended the specification to recite specific panel names in those drawings which contain multiple panels.

Maintained Rejections and Objections

Specification

5. The disclosure is objected to because of the following informalities:

1) Typographical errors "Mol", "Nat'l.", and nrocesses (paragraph 0006)

2) Typographical error "Enzymolo^{9}y" (paragraph 0015)

3) Typographical error "FIG 1 IIIIlustrates" (paragraph 0030)

4) Typographical error "▪ - lacatamase" (paragraph 0066)

5) Typographical error "Ni"" (paragraph 0130)

Appropriate correction is required.

New Rejections and Objections

Claim Objections

6. Applicant is advised that should claim 1 be found allowable, claims 3 and 6 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

7. Applicant is advised that should claim 10 be found allowable, claims 12 and 15 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

8. Claims 1 – 4, 6 – 13, and 15 – 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administration of anti-MPC-1 receptor antibodies, does not reasonably provide enablement for inhibition of any condition characterized by monocytic infiltrates. The specification does not enable any person skilled in the art to which

it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In the previous office action the examiner had indicated that the specification was enabling for an antibody or a binding fragment thereof which binds to an MCP-1 receptor. Upon further consideration, the specification is only deemed enabling for intact antibodies which bind to the full length MCP-1 receptor with either SEQ ID NO:2 or SEQ ID NO:4.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

The nature of the invention, methods of inhibiting conditions characterized by monocytic infiltrates, is complex. The art indicates that there are a wide variety of chemokines and receptors, and that the interactions between receptors and their ligands is very complex, given that some receptors signal and others don't, and that there can be cross-talk between various receptor systems. See Sheikine et al. (2004) Annals of Medicine 36:98 – 118, particularly pages 100 – 104.

The specification does not provide guidance as to how to make fragments of antibodies which bind to MCP-1 receptor and are sufficient to inhibit conditions characterized by monocytic infiltrates. Specifically, the specification does not disclose a relationship between particular structural elements of the MCP-1 receptor and the desired functions, i.e. which regions of the receptor must be bound in order for the claimed method to work. MCP-1 receptor is a complex molecule with seven transmembrane domains (see specification, p. 30, paragraph 0103, and Figure 4). There is not sufficient guidance to allow a skilled artisan to conclude that antibodies which bind the transmembrane domains, for example, will inhibit conditions characterized by monocytic infiltrates or will inhibit the protein. The art recognizes that the family of G-protein coupled receptors (GPCRs), of which MCP-1 receptor is a member, need to bind ligands in order to become active (see Ji et al. 1998. Journal of Biological Chemistry 237:17299-17302). Since the claims are drawn to methods of inhibiting MCP-1 receptor polypeptide (see claim 9, for example), the activity of the receptor must be inhibited. However applicant has not shown

which regions of the receptor are crucial for the activities most frequently associated with GPCRs, namely ligand binding and signaling. Furthermore Ji et al. teach that different GPCRs use different regions for ligand binding (see p. 17301, for example). Therefore a disclosure that MCP-1 receptor is a GPCR is not sufficient to identify the regions critical to its function, or inhibiting said function. The prior art publication by Monteclaro et al. (1997. Journal of Biological Chemistry 272:23186-23190) clearly disclose which regions of the receptor are necessary and sufficient for binding to MCP-1.

Applicant has not provided sufficient guidance in the specification for methods of making antibodies which are effective in the claimed methods, but which bind to less than the full-length MCP-1 of SEQ ID NO:2 or 4. Furthermore, applicant has not provided sufficient guidance as to what fragments of antibodies are necessary for the claimed methods. The art recognizes that Fab (fragment antigen binding) fragments are well-known (see for example Alberts et al. 1994. Molecular Biology of the Cell, pp. 1208 – 1209), but claims 1, 6, 10, and 15 recite the limitation "binding fragment thereof", which appears to be of a different scope than Fab fragments. There are no working examples of administration of antibodies to MCP-1 receptor to patients. Furthermore, the specification does not provide sufficient guidance to allow a skilled artisan to know how to identify conditions characterized by monocytic infiltrates. Therefore the artisan would be required to undertake undue experimentation; he would have to identify patients with various conditions, then obtain relevant tissue samples, determine the number of monocytes, determine whether those monocytes are normally present or are infiltrating the tissue, compare the tissue samples to samples taken from patients without the condition, and finally make a determination whether or not the condition is characterized by monocytic infiltrates.

Claims 1 and 10 both recite the limitation "therapeutically effective amount". But since a skilled artisan would have to resort to undue experimentation just to find which conditions are characterized by monocytic infiltrates, he certainly would have to resort to undue experimentation to then determine a therapeutically effective amount of the antibody to be administered. The specification does not provide sufficient guidance to allow the artisan to determine how to tell what doses are effective, and thus the artisan would essentially have to rely on trial-and-error experimentation, particularly in light of the lack of predictability of treatment of diseases with antibodies.

The art recognizes that the treatment of diseases with antibodies is unpredictable. Applicant is directed to the enclosed publications by Harris et al. (1993. Therapeutic antibodies

– coming of age. Trends in Biotech 11:42 – 44, see particularly page 42) and Seaver (1994. Monoclonal antibodies in industry: more difficult than originally thought. Genetic Engineering News 14:10 and 21; see particularly page 10, columns 3 and 4).

Because of the lack of guidance in the specification, the lack of working examples drawn to inhibiting conditions characterized by monocytic infiltration by administration of antibodies, the complex nature of the invention, the unpredictability of the art, and the breadth of the claims, it would take undue experimentation on the part of a skilled artisan to make and use the claimed invention.

9. Claims 1 – 4, 6 – 13, and 15 – 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

In the instant case, the claims are drawn to methods of treating diseases or inhibiting MCP-1 receptor polypeptide by administering a pharmaceutical composition comprising an antibody or "binding fragment," which specifically binds MCP-1 receptor. This is a broad generic term which encompasses a wide variety of antigen binding fragments. The instant disclosure of the antibody which specifically binds MCP-1 receptor polypeptide, does not adequately describe the scope of the use of "binding fragment thereof" or wherein said binding inhibits certain conditions or the polypeptide.

A description of a genus may be achieved by means of a recitation of a representative number of species, defined by a specific structure and/or function, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. A genus claim may be supported by a representative number of species as set forth in Regents of the University of California v Eli Lilly & Co, 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

The instant specification fails to provide sufficient descriptive information, such as definitive structural and functional features of the binding fragments and/or wherein said binding results in neutralization of activity. There is no description of the conserved regions, which are critical to the structure and function of the genus claimed. Structural features that could distinguish the binding fragment in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to identify the binding fragment encompassed. No identifying characteristic or property of "binding fragment" and/or wherein such results in neutralization of activity are provided such that one of skill would be able to predictably identify the encompassed fragments as being identical to those instantly claimed.

Vas-cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-cath, page 1116).

10. Claims 1 – 4, 6 – 13, and 15 – 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The following recitations are not supported within the specification and priority documents. As a Continuation, the instant application must have support for the subject matter in the parent applications. No support in the parent applications (Application Nos.: 09/625,573, 08/446,669, and 08/182,962) can be found for the following limitations recited in the claims [see MPEP §608.04(a)]:

a. claims 1 and 10, "binding fragment thereof"

b. claims 4 and 13, "about 10 ug/ml to about 1 mg/ml"

c. claims 7 and 16, "monoclonal antibody"

d. claims 8 and 17, "humanized antibody"

e. claim 10, "method for inhibiting MCP-1 receptor polypeptide". Applicant is advised that there is support for inhibition of the activation of MCP-1 receptor, as measured with mobilization

of intracellular calcium and activation of adenylyl cyclase, on page 43, lines 1 – 20, of application 08/446669, however there does not appear to be support for inhibiting the polypeptide.

The presentation of the above subject mater in the original claims of the instant Application constitutes the introduction of **New Matter**. This is not permitted in the filing of a Continuation under 35 U.S.C. 120 [see MPEP §201.07 and 201.08]. There is neither ipsis verbis support for, nor contemplation of, the terms in the specification as originally filed, or in the applications to which the instant application claims priority.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1 – 4, 6 – 13, and 15 – 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 6, 10, and 15 recite the term "antibody or binding fragment thereof". The term "binding fragment" is indefinite because it can be interpreted as meaning Fab fragments, which are well-known in the art, or other fragments of the antibody which bind to the antigen, or fragments of the antibody which can be bound by another compound, for example by a second antibody in an immunoassay. The remaining claims are rejected because they depend from claims 1 and 10, which are themselves confusing and indefinite.

Claim Rejections - 35 USC §§ 102 and 103

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 1 – 3, 6 – 12, and 15 – 17 are are rejected under 35 U.S.C. 102(b) as being anticipated by LaRosa et al. (U.S. Patent 6,312,689, cited by applicant on IDS filed 20 May 2005). LaRosa et al. teach antibodies to MCP-1 receptor, which is also known by the following synonyms: CCR2, CKR-2, MCP-1RA, and MCP-1RB as well as fragments thereof which bind to CCR2 (column 2, lines 20 – 41) and administration of the antibodies as pharmaceutical compositions (column 26, lines 22 – 57). LaRosa et al. also teach that the antibodies and functional fragments thereof can be used to inhibit specific functions of MCP-1 receptor (i.e. CCR2; see column 2 lines 8 – 12). Therefore the teachings of LaRosa meet the limitations of claims 1, 3, 6, 10, 12, and 15.

LaRosa et al. teach that their antibodies bind to human CCR2, particularly naturally occurring CCR2 (column 6, lines 46 – 50). Applicant has disclosed that SEQ ID NO:2 and 4 are natively-occurring human sequences (specification, p. 5, paragraph 0009); therefore the antibodies of LaRosa et al. will inherently bind to SEQ ID NO:2 and 4, as both applicant and LaRosa use antibodies which bind to naturally-occurring human CCR2 (i.e. MCP-1 receptor). Therefore the teachings of LaRosa et al. also meet the limitations of claims 2 and 11.

LaRosa et al. also teach both monoclonal antibodies (see column 7, lines 25 – 60) and humanized antibodies (see column 9 line 10 – column 10 line 56), meeting the limitations of claims 7, 8, 16, and 17. LaRosa et al. teach that their antibodies are used to treat atherosclerosis (column 23 lines 35 – 64), meeting the limitations of claim 9.

15. Claims 4 and 13 are rejected under 35 U.S.C. 103(a) as obvious over LaRosa et al. As described in the preceding paragraphs, the teachings of LaRosa et al. meet the limitations of claims 1 and 10. LaRosa et al. do not teach the specific concentration of the antibody used in their pharmaceutical composition. However optimization of the concentration or dosage unit of a pharmaceutical composition is considered routine for one of ordinary skill in the art.

Conclusion

16. No claim is allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on (571) 272-0829. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel E. Kolker, Ph.D.
June 23, 2005

Brenda Brumback
BRENDA BRUMBACK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600